Simplicity is key in CRT

Valorization

About 1-2% of the adult population in developed countries suffers from heart failure (HF). (1) Of these patients 36% has a significantly reduced ejection fraction (≤35%). (2) Despite advances in therapy, HF has a poor prognosis. One-year all-cause-mortality in patients with HF is 7%, and reaches 17% in patients hospitalized for HF. Hospitalization rate is 32% per year (3), and patients experience a significantly reduced quality of life. Cardiac resynchronization therapy (CRT) has been shown to be able to reduce mortality and HF-hospitalizations significantly (by approximately 25% and 40%, respectively), and to significantly improve quality of life of the patients. (4)

CRT aims at treating HF patients in which electrical conduction disorders contribute to, or cause HF with a reduced ejection fraction. When applying current guidelines (HF with reduced ejection fraction, wide QRS complex) approximately 10% of all HF patients could be considered for CRT. (5)

Although CRT provides great reductions in HF burden on a population level, the benefit at the level of the individual patient varies significantly. Studies show a great benefit from therapy in 50-70% of patients but worsening in up to 22%. (6, 7) As CRT entails the implantation of a costly biventricular pacemaker or ICD device, the risk of procedural complications, and the need of intensive follow-up and future invasive procedures, patient selection and management in CRT are of great importance.

Patient selection

In **part I** of this thesis we have shown that the most important recommended 12-lead ECG parameter used in patient selection for CRT, left bundle branch block (LBBB), has important limitations. Guidelines embrace this marker with high levels of evidence, based on several substudies of large randomized trials. However, guidelines neglect to take into account the existence of multiple LBBB definitions, and the overall subjectivity in judgement of the QRS morphology. We have demonstrated that the interpretation of LBBB-patterns on the 12-lead entails great inter-observer and inter-definition variability and has a poor (no more than moderate) association with clinical interpretation by experienced implanters. These findings question the applicability of the results of the aforementioned clinical trials on clinical practice.

Because of the great variability found in aforementioned analysis, we have investigated the associations of each of the available LBBB definitions' associations to outcome in CRT patients. We confirm that patients, qualified as LBBB according to any definition have significantly better outcomes to CRT, compared to those qualified as non-LBBB patients. However, the analyses in this thesis also show that the available LBBB definitions entail morphological criteria not relevant to patient selection in CRT. Therefore, LBBB definitions may be unnecessarily complex, perhaps leading to the abovementioned variability. In a quest to improve the prediction of benefit from CRT in patients, we have designed a novel outcome based LBBB definition, consisting of the morphological criteria that proved to be independently associated with CRT outcome in our retrospective cohort analysis. However, this outcome-based definition did not improve diagnostic yield. Therefore, it appears that the morphological features of ventricular activation, displayed on the 12-lead ECG, are not able to further improve patient selection.

In order to help improve patient selection, we have explored a novel ECG-derived marker of dyssynchrony. After synthesis of the vectorcardiogram from the 12-lead ECG, the QRS area was calculated and, in a large patient cohort, evaluated for its' association with outcome to CRT. Our findings greatly support earlier small studies showing a strong association of QRS area with clinical and echocardiographic outcome to CRT. In the analysis presented, QRS area improved prediction of outcome over the currently recommended combination of LBBB and QRS duration. Furthermore, QRS area is especially of value as is provided significant separation in patients with better and worse outcome in the subgroup of non-LBBB QRS morphology, a group in which the application of CRT is currently debated (Guideline IIa and b recommendations). (1)

Application of QRS area in clinical practice and recommendation of its use in the prevailing guidelines would require the prospective evaluation of QRS area appended or replacing current patient selection parameters. However, as the value of current markers has been shown in subanalyses of the landmark randomized controlled trails, it seems realistic to evaluate QRS area in the same way. This is currently being performed in data from the RAFT study. (8) Furthermore, while LBBB patients already have a class I recommendation for CRT implantation, adding QRS area to the selection for CRT could improve specificity, denying non-responders CRT. However, use of QRS area in the currently disputed indications in non-LBBB patients could uncover potential responders who are currently not selected for CRT. For the latter purpose, our group is currently starting a prospective observational multimarker study (MARC-2 study) focussing on non-LBBB patients.

For the analyses presented in this thesis, QRS area was calculated using custom-made software to converge vectorcardiographic data and the QRS area algorhythm from the original digital 12-lead ECG signals. An important step towards a wider clinical use of QRS area is to program the algorithm for its calculation into ECG machines. When, indeed QRS area can be calculated automatically and its value will be further established, it may be possible that QRS area replaces LBBB morphology and QRS duration as ECG markers for patient selection in CRT. Such use would avoid the subjectivity and variability involved in defining LBBB morphology, **'simplifying'** patient selection and increasing prediction of outcomes to CRT.

Patient management

Apart from selecting the patient able to benefit from CRT, implantation of the biventricular pacemaker or ICD device, follow-up, and general patient management in all steps involved in CRT for HF is of great importance. The patient will be followed for both HF disease management and resynchronization therapy or device management. These properties are generally specialties of several different health care providers. Furthermore, studies have shown a wide range of device- and HF-related factors related to suboptimal benefit from CRT. (9-11) CRT patient management therefore is comprehensive and complex, and often entails many health care providers' contacts and additional investigations. In this thesis we presented a blue print 'CRT care pathway', combining the knowledge of experienced health care providers into a streamlined process. This blueprint allows clinics involved in care for HF patients treated with CRT to compare their current patient management process and add steps or checks essential, or instead cut 'waste', for optimal patient management, with minimal health care and patient burden. Furthermore, we shown the process of implementation into the Maastricht University Medical Centre + and the reorganization involved in introducing the CRT care pathway into the existing CRT patient care. All together **part II** of this thesis provides the tools to introduce a structured care pathway in any CRT follow-up clinic, and implement it into current care. Although

the evaluation of these changes has not yet finished, and therefore the benefit for both patients and clinic have not been proven, patients and health care providers' feedback are encouraging. Multidisciplinary CRT programs have been studied and found effective before. (9, 12) The average clinic does not have the resources available to change their CRT follow-up practice into the programs evaluated in these studies as they entail the addition of expertise or resources. The presented CRT care pathway, however aims to increase patient benefit from CRT, as well as decrease patient and health care burden. When evaluation of the care pathway proves to increase patient benefit and/or reduce patient and health care burden, the research presented here will allow for easy implementation into any clinic interested in improvement of their care for heart failure patients treated with CRT.

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